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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/465,133	12/15/1999	ELISABETTA VEGETO	246/180	8491

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	09/465,133	VEGETO ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *144-192* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *144-192* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/5/04, 3/22/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 144-192 are pending in the application.

This Office Action is in response to the Amendment filed on 3/22/04.

Response to Amendment

The rejection of claims 100-105, 107, 108, 111-123, 127, 129-143 under 35 U.S.C.101 and 112 1st paragraph is moot in light of Applicant's cancellation of the claims.

The rejection of claims 168-176 under 35 U.S.C. 112 2nd paragraph has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 144-168 under 35 U.S.C.112 1st paragraph (written description) is maintained for reasons set forth of the record mailed on 3/11/03 and further discussed below.

The rejection of claims 144-192 under 35 U.S.C. 112 1st paragraph (scope of enablement) is maintained for reasons set forth of the record mailed on 3/11/03 and further discussed below.

Claims 168-176 are rejected under 35 U.S.C. 112 2nd paragraph for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 144-168 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants did not respond to this rejection. Therefore, this rejection is maintained for same reasons set forth of the record mailed on 3/11/03.

Claims 144-192 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of regulating gene expression transiently *in vivo* by either a) introducing into a wild type animal a construct encoding a progesterone receptor with at least 42 amino acid deletion from C-terminal, and another construct comprising a progesterone receptor responsive element linked to a report gene; b) administering a ligand that binds to said mutated receptor to said animal, or administering a ligand that binds to a mutated steroid receptor to a transgenic non-human animal, wherein said transgenic non-human animal expresses a heterologous reporter gene and a mutated steroid receptor, wherein expression of said receptor regulates the expression of the reporter gene by binding to the promoter of said reporter gene, does not reasonably provide enablement for said method utilizing any transgenic animal or long term expression in any animal, and/or any mutated steroid hormone receptor that is capable of binding ligand that is an antagonist of the natural occurring receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In response to this rejection, Applicants argue that the present invention is valuable in transgenics where it permits the study of genes whose expression would be lethal during development. Applicants cite Wang et al. (2002) to demonstrate the application of the claimed invention to transgenic mouse for regulated expression in which the transgene was readily

induced by ligand administration *in vivo*. Applicants further cited Bockamp et al. which reiterate the particular advantages of the steroid hormone receptor switch in transgenic applications. Applicants assert that the generation of transgenic animals is well known at the time of filing, thus no undue experimentation is required. Applicants further argue that long-term expression can be achieved by constitutive expression in a tissue specific manner for the life of the animal. Moreover, Applicants argue that transient expression can be long term as demonstrated by Nordstrom reference. Furthermore, Applicants argue that the specification teaches the generation of molecular switches based on other steroid hormone receptors other than the progesterone receptor. In addition, Branchen et al. demonstrate the generation of mutated estrogen receptor that can serve as molecular switch, whereas Lanz et al. demonstrate the generation of glucocorticoid receptor mutant. Lastly, Applicants argue that claims 177-192 relate to a specific embodiment in which the steroid hormone receptor is a progesterone receptor having an alteration in one or more of the C-terminal 54 amino acids, which is fully supported by the instant specification. Applicants thus conclude that the claimed invention is enabled to its full scope.

These arguments have been fully considered but deemed unpersuasive. Although generating transgenic animals at the time of filing is well known in the art, the phenotype of the transgenic animal cannot be predicted before the transgenic animal has been made. As such, only transgenic non-human animals express a heterologous reporter gene and the molecular switch is enabled by the instant specification because the specification does not teach how to use the transgenic animals with the claimed genotype but fail to express the switch and the reporter gene. The cited references do not teach how to use such transgenic animal either. Therefore, the

claimed invention is enabled to the scope wherein the transgenic animal expresses both the molecular switch and the reporter protein.

The examiner acknowledges that long-term expression can be achieved by expressing the genes in a transgenic animal and its progeny; however, the scope is limiting claims direct to transient expression of the molecular switch and the reporter protein. In fact, all claims encompass such limitation because an animal comprising the molecular switch cassette is not limited to transgenic animal, they encompass transgenic animal and animals have been administered with the construct. With regard to the Nordstrom reference, Applicants are reminded that the claimed invention must be enabled at the time the invention was made. Nordstrom reference was published in 2003, 11 years after the filing date of the instant application. As such, it cannot be solely relied on to support the enablement of the claimed invention.

Contrary to Applicants' assertion, the specification does not teach the generation of a molecular switch using other steroid receptor but only a single progesterone receptor molecular switch. As discussed in the previous office, a single example of deletion of 42 C-terminus amino acids from the progesterone receptor cannot extend the predictability of its function in other members of the receptor family or other types of mutation of the receptors. The teaching of the structure of the wild type receptor that 300 amino acid is responsible for binding of ligand is not sufficient to support the notion that any mutation within this region would make it a molecular switch as claimed. In fact, the specification teaches that it is difficult in distinguishing among amino acid residues that affect the overall structure of this domain from those directly involved in a direct contact with the ligand because this binding domain folds into a complex tertiary

structure. Therefore, whether any mutation in this region in any steroid receptor would result in a molecular switch as claimed is unpredictable. The subsequent of generation of estrogen receptor by Branchen and glucocorticoid receptor switch by Lanz is resulted from trial and error rather than routine experimentation. Therefore, these references do not support the notion that any steroid receptor molecular switch can be generated based on the teaching of the specification. In fact, Lanz teaches that mutations in rat glucocorticoid receptor not necessarily generate such molecular switch (see abstract). Therefore, whether any mutation in the ligand binding domain in any steroid receptor can generated a molecular switch is unpredictable.

With regard to claims 177-192, the specification does not provide support for the enablement to the full scope. Applicants acknowledge that 54 and 42 amino acid deletions from the C-terminal of progesterone receptor are taught in the specification, however, whether mutation of any kind (including single substitution, deletion of 1 or 2 amino acid from this region) of 1-54 amino acid in this region would result in the molecular switch as claimed is unpredictable. The specification does not teach whether other mutation within this region can result in the claimed molecular switch. The art does not teach such information either. Without guidance from the specification, one skilled in the art would have to engage in undue experimentation to practice the method as claimed. Therefore, the claimed invention is not enabled to its full scope.

New Grounds of Rejection Necessitated by Applicants' Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 168-176 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "administering to the animal a pharmacological dose of a ligand that activates a molecular switch expression vector, the cassette ... or is comprised in a non-human transgenic animal" renders the claims indefinite because it is unclear whether the ligand and the molecular switch expression vector are located within same animal. In other words, if the cassette in a non-human transgenic animal, it is unclear how the ligand administered to another animal can activate said switch. Appropriate clarification is required.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER